Journal of the American Heart Association

ORIGINAL RESEARCH

Label Adherence of Direct Oral Anticoagulants Dosing and Clinical Outcomes in Patients With Atrial Fibrillation

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BACKGROUND: Dose adjustment of non-vitamin K antagonist oral anticoagulants (NOACs) is indicated in some patients with atrial fibrillation (AF), based on selected patient factors or concomitant medications. We assessed the frequency of label adherence of NOAC dosing among AF patients and the associations between off-label NOAC dosing and clinical outcomes.

METHODS AND RESULTS: We evaluated 53 649 AF patients treated with an NOAC using Korean National Health Insurance Service database during the period from 2013 to 2016. NOAC doses were classified as either underdosed or overdosed, consistent with Korea Food and Drug Administration labeling. Cox proportional hazards regression was performed to investigate the effectiveness and safety outcomes including stroke or systemic embolism, major bleeding, and all-cause mortality. Overall, 16 757 NOAC-treated patients (31.2%) were underdosed, 4492 were overdosed (8.4%), and 32 400 (60.4%) were dosed appropriately according to drug labeling. Compared with patients with label adherence, those who were underdosed or overdosed were older (aged 71±8 and 75±7 years versus 70±9 years, respectively; $P<0.001$) and had higher CHA_2DS_2-VASc scores (4.6±1.7 and 5.3±1.7 versus 4.5±1.8, respectively; $P<0.001$). NOAC overdosing was associated with increased risk for stroke or systemic embolism (5.76 versus 4.03 events/100 patient-years, $P<0.001$), major bleeding (4.77 versus 2.94 events/100 patient-years, $P<0.001$), and all-cause mortality (5.43 versus 3.05 events/100 patient-years, $P<0.001$) compared with label-adherent use.

CONCLUSIONS: In real-world practice, a significant proportion (almost 2 in 5) of AF patients received NOAC doses inconsistent with drug labeling. NOAC overdosing is associated with worse clinical outcomes in Asian AF patients.

Key Words: atrial fibrillation ■ label adherence ■ non-vitamin K antagonist oral anticoagulants ■ overdosing ■ underdosing

The prevalence of atrial fibrillation (AF) is rapidly increasing globally, especially in the Asian population,[1,2] and oral anticoagulation (OAC) is the principal management for stroke prevention in patients with AF.[3,4] The efficacy and safety of the non-vitamin K antagonist oral anticoagulants (NOAC) have all been shown at least as effective and safe as warfarin in large randomized controlled trials.[5–8]

Dose adjustment of NOACs is indicated in some AF patients, based on selected patient factors such as renal function, age, body weight, or concomitant medications.[9] However, whether these dose recommendations are adhered to in community practice remains a major concern. In a study with ORBIT-AF II (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II) database,[10] NOAC over- and underdosing

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Supplementary Materials for this article are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014177

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For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The real-world label adherence of non-vitamin K antagonist oral anticoagulants (NOAC) dosing across all 4 NOACs and their clinical effects in Asian atrial fibrillation patients were investigated.
- Of those treated, only 60% of patients were dosed appropriately, with 30% of patients underdosed in real-world practice.

What Are the Clinical Implications?

- NOAC overdosing was associated with increased risk for adverse outcomes compared with label-adherent dosing.
- There was no safety benefit of underdosing compared with the appropriate dosing of NOACs.
- Label adherence of NOAC dosing is important to improve the clinical outcomes in atrial fibrillation patients.

Nonstandard Abbreviations and Acronyms

AF	atrial fibrillation
OAC	oral anticoagulation
NOAC	non-vitamin K antagonist oral anticoagulants
NHIS	national health insurance system
ICD-10	*International Classification of Diseases, Tenth Revision*

were shown to be associated with increased risk for adverse events. In addition, a previous study using a large US administrative database with about 15 000 AF patients revealed that the prescribed doses were often inconsistent with the renal dose recommendation by Food and Drug Administration labeling.[11] In that study, inappropriate dose reduction was related to reduced effectiveness for stroke prevention without any safety benefit. Recently, we reported the real-world effectiveness and safety of edoxaban in Korean AF patients in relationship to renal function.[12] Interestingly, low-dose edoxaban had lower effectiveness for stroke prevention compared with warfarin at higher levels of creatinine clearance, which is called super normal renal function.

Therefore, in the current study, we sought to assess the frequency of label adherence of NOAC dosing among Korean AF patients, and to analyze the associations between off-label NOAC dosing and clinical outcomes in real-world clinical practice.

METHODS

Data Source

This study is based on the national health claims database established by the national health insurance system (NHIS) of Republic of Korea.[13,14] The NHIS is the single insurer managed by the Korean government, and the majority (97.1%) of the Korean population are mandatory subscribers, with the remaining 3% of the population being medical aid subjects. The NHIS database contains the information of medical aid subjects, therefore it is based on the entire Korean population. All data and materials have been made publicly available at the National Health Insurance Sharing Service and can be accessed at (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do).

The NHIS also provides regular health check-up programs for the public. Subscribers of the NHIS are recommended to undergo this check-up at least biennially, and it includes blood tests, chest X-ray examinations, physical examinations of the patients, and questionnaires on their medical history. Every population in the NHIS database was linked by the Korean social security numbers, and all social security numbers were deleted after constructing the cohort by giving serial numbers to prevent leakage of personal information. This study was approved by the Institutional Review Board of Yonsei University Health System (4-2016-0179), and informed consent was waived.

Study Population

We identified a total of 866 363 patients with prevalent AF who were aged ≥18 years from January 1, 2013 to December 31, 2016. AF was diagnosed using the *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes, I48 (AF and atrial flutter), I48.0 (AF), and I48.1 (atrial flutter). Moreover, patients were diagnosed with AF only when it was a discharge diagnosis or confirmed more than twice in the outpatient department to ensure diagnostic accuracy.[15] The diagnosis of AF has previously been validated in the NHIS database with a positive predictive value of 94.1%.[16–18] Definitions of other comorbidities are presented in Table S1. The following were exclusion criteria: (1) those with valvular AF (with a diagnosis of mitral stenosis [*ICD-10*: I05.0, I05.2, and I34.2] or prosthetic heart valves [*ICD-10*: Z95.2–Z95.4], and insurance claims for valve replacement or valvuloplasty) (n=8646), (2) those who ever underwent catheter ablation (n=5607), (3) those ever diagnosed with end-stage renal disease (n=933), (4) no OAC or OAC use <30 days (n=717 946), (5) OAC use for acute coronary syndrome or deep vein thrombosis prophylaxis (n=4188), or (6) warfarin users (n=34 851) (Figure 1).

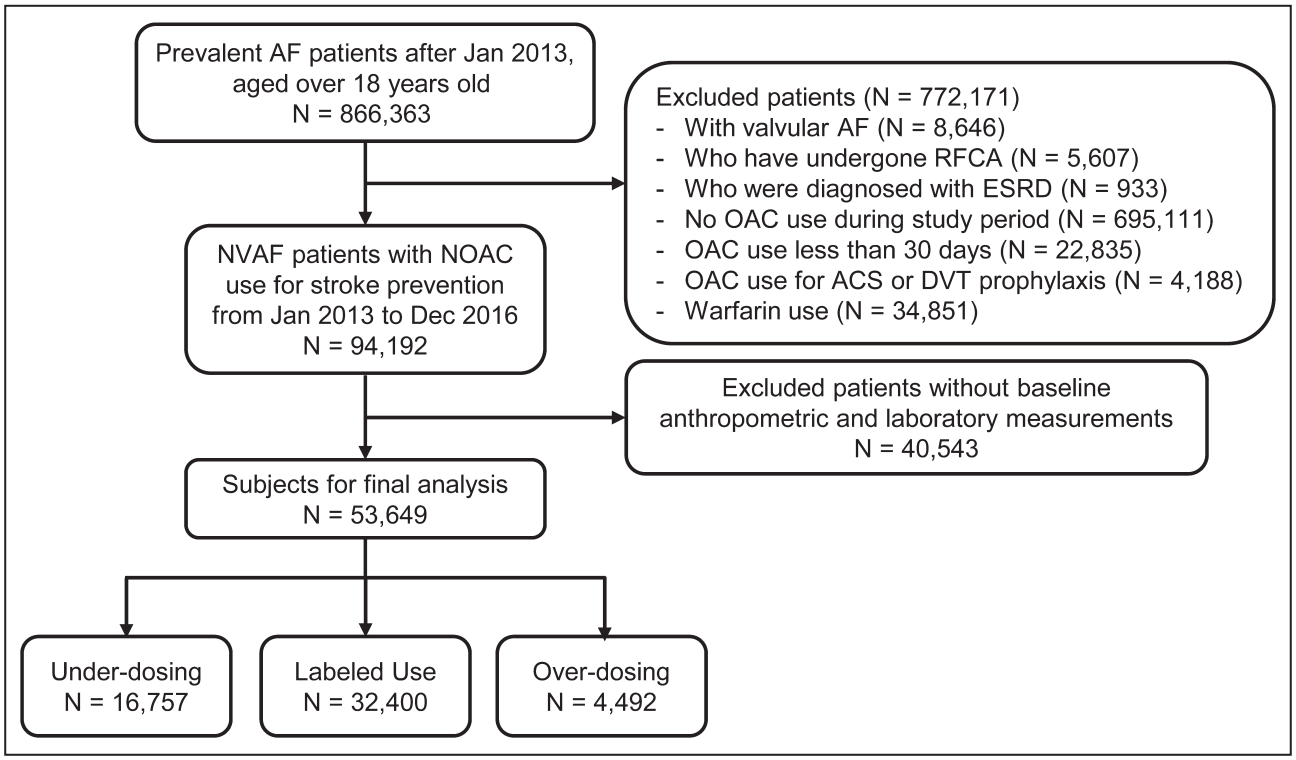

Figure 1. Flowchart of study population enrollment.
ACS indicates acute coronary syndrome; AF, atrial fibrillation; DVT, deep vein thrombosis; ESRD, end-stage renal disease; NOAC, non-vitamin K antagonist oral anticoagulants; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulants; and RFCA, radiofrequency catheter ablation.

Among the 94 192 patients, patients without baseline anthropometric and laboratory measurements for evaluation of compliance with labeled dosing were excluded (n=40 543). Finally, we identified 53 649 non-valvular AF patients in this study. We defined the date of the first oral anticoagulant prescription as the index date. The follow-up period was defined as from the index date until the first occurrence of any study outcome or the end date of the study period (December 31, 2016), whichever came first.

NOAC Dose Reduction Criteria and Dosing According to Label

A standard dose was defined, according to each NOAC, as dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily, apixaban 5 mg twice daily, and edoxaban 60 mg once daily. Approved dose reduction criteria were specific to each NOAC, according to the following patient characteristics: age, body weight, serum creatinine level at the patients' enrollment, and concomitant medications. Creatinine clearance was calculated using the Cockcroft-Gault equation. The adherence with labeled dosing of each NOAC in each study patient was evaluated based on the Ministry of Food and Drug Safety labeling (Table S2). Patients were categorized into 3 groups based on NOAC dose and dose recommendation adherence: labeled use (n=32 400), underdosing (n=16 757), and overdosing (n=4492).

Study Outcomes

The primary study outcomes were stroke or systemic embolism, major bleeding, and death from any cause. Secondary outcomes were intracranial bleeding, gastrointestinal bleeding, and myocardial infarction. The clinical events that occurred after 1 week of quarantine periods after initial OAC prescription were counted as the study outcomes. The *ICD* codes for the study outcomes are summarized in Table S3. Data on vital status and date of death were reconfirmed, and the cause of death was determined from the National Population Registry of the Korea National Statistical Office with the use of a unique personal identification number, in which central registration of death was conducted on the basis of death certificates.[19] This approach provides a complete event ascertainment.

Statistical Analysis

Continuous variables were presented as means and standard deviations. Comparison of continuous variables was performed using an independent t test or, in case of a non-normal distribution, the Mann–Whitney

Table. Baseline Characteristics

	Overall (n=53 649)	Underdosing (n=16 757)	Labeled Use (n=32 400)	Overdosing (n=4492)	*P* Value
Age, y	70.5±8.9	70.7±7.9	69.8±9.5	74.8±7.2	<0.001
Age <65 y	11 699 (21.8)	3086 (18.4)	8273 (25.5)	340 (7.6)	<0.001
65≤ Age <75 y	22 763 (42.4)	7809 (46.6)	13 302 (41.1)	1652 (36.7)	<0.001
Age ≥75 y	19 187 (35.8)	5862 (35.0)	10 825 (33.4)	2500 (55.7)	<0.001
Men	32 350 (60.3)	10 230 (61.0)	20 016 (61.8)	2104 (46.8)	<0.001
Comorbidities					
Heart failure	32 845 (61.2)	10 257 (60.4)	19 574 (60.4)	3014 (67.1)	<0.001
Hypertension	50 921 (96.3)	15 966 (95.3)	30 629 (94.5)	4326 (96.3)	<0.001
Diabetes mellitus	16 952 (31.6)	5406 (32.3)	10 189 (31.4)	1357 (30.2)	0.021
Stroke or TIA	24 411 (45.5)	6968 (41.6)	15 096 (46.6)	2347 (52.2)	<0.001
Vascular disease	15 443 (28.8)	4983 (29.7)	9045 (27.9)	1415 (31.5)	<0.001
Previous MI	6285 (11.7)	2096 (12.5)	3625 (11.2)	564 (12.6)	<0.001
PAD	10 935 (20.4)	3476 (20.7)	6443 (19.9)	1016 (22.6)	<0.001
CKD	4354 (8.1)	1279 (7.6)	2613 (8.1)	462 (10.3)	<0.001
Dyslipidemia	49 406 (92.1)	15 464 (92.3)	29 773 (91.9)	4169 (92.8)	0.055
CHA_2DS_2-VASc score	4.6±1.8	4.6±1.7	4.5±1.8	5.3±1.7	<0.001
NOAC type					
Dabigatran	16 379 (30.5)	6428 (38.4)	8934 (27.6)	1017 (22.6)	<0.001
Rivaroxaban	20 143 (37.5)	5426 (32.4)	12 332 (38.1)	2385 (53.1)	<0.001
Apixaban	11 933 (22.2)	4002 (23.9)	7673 (23.7)	258 (5.7)	<0.001
Edoxaban	5194 (9.7)	901 (5.4)	3461 (10.7)	832 (18.5)	<0.001
Other medication use					
Aspirin	8714 (16.2)	2916 (17.4)	5079 (15.7)	719 (16.0)	<0.001
$P2Y_{12}$ inhibitors	5005 (9.3)	1766 (10.5)	2792 (8.6)	447 (10.0)	<0.001
ACEi/ARB	27 535 (51.3)	8537 (50.9)	16 714 (51.6)	2284 (50.8)	0.323
Beta-blockers	30 773 (57.4)	9698 (57.9)	18 589 (57.4)	2486 (55.3)	0.010
CCBs	9875 (18.4)	3173 (18.9)	5869 (18.1)	833 (18.5)	0.081
Digoxin	9766 (18.2)	3117 (18.6)	5617 (17.3)	1032 (23.0)	<0.001
Diuretics	24 852 (46.3)	7866 (46.9)	14 632 (45.2)	2354 (52.4)	<0.001
Statins	31 067 (57.9)	9560 (57.1)	18 917 (58.4)	2590 (57.7)	0.017
AAD (class Ic)	8730 (16.3)	2657 (15.9)	5590 (17.3)	483 (10.8)	<0.001
AAD (class III)	5838 (10.9)	1697 (10.1)	3614 (11.2)	527 (10.9)	<0.001

Values are mean±SD or n (%). AAD indicates anti-arrhythmic drug; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCBs, calcium channel blockers; CKD, chronic kidney disease; MI, myocardial infarction; PAD, peripheral artery disease; and TIA, transient ischemic attack.

test. Categorical variables were represented with numbers and percentages using the Chi-square test of Fisher exact test. Incidence rates were estimated using the total number of study outcomes during the follow-up period divided by person-years at risk. The risk for clinical outcomes for study groups were obtained using survival analysis (Kaplan–Meier method and log-rank test for univariate analysis and Cox proportional hazards regression for multivariate analysis). Cox proportional hazards regression was used to estimate the unadjusted and adjusted hazard ratio for the association between label adherence of NOAC dosing and clinical outcomes. To control for confounding, we added age, sex, chronic kidney disease, dyslipidemia, and other risk factors included in CHA_2DS_2-VASc risk score factors (heart failure, hypertension, diabetes mellitus, stroke or transient ischemic attack, and vascular disease) to our multivariable models. Statistical significance was indicated by a $P<0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and SPSS version 23.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics

Baseline characteristics of study population are presented in Table. We evaluated 53 649 AF

patients treated with NOACs (dabigatran 30.5%, rivaroxaban 37.5%, apixaban 22.2%, and edoxaban 9.7%). The mean age was 70.5±8.9 years, 60.3% were men, and the mean CHA_2DS_2-VASc score was 4.6±1.8. Four thousand three hundred fifty-four (8.1%) patients had chronic kidney disease at baseline, and 16.2% and 9.3% of patients were prescribed concomitant aspirin and P2Y12 inhibitors, respectively.

Label Adherence of NOAC Dosing

In the total study population, 31% NOAC-treated patients were underdosed, 8.4% were overdosed, and 60% were dosed appropriately according to drug labeling. (Table) The overdosing group were older (74.8±7.2 years versus 69.8±9.5 years in labeled use group and 70.7±7.9 years in underdosing group), tended to be women (53.2% versus 38.2% in labeled use group and 39.0% in underdosing group), and had a higher CHA_2DS_2-VASc score (5.3±1.7 versus 4.5±1.8 in labeled use group and 4.6±1.7 in underdosing group) than the other groups. Patients taking dabigatran or apixaban were prescribed with underdosing more frequently than those taking rivaroxaban or edoxaban, whereas patients taking rivaroxaban or edoxaban were more frequently prescribed with overdosing than those taking dabigatran or apixaban (Figure 2).

Clinical Outcomes According to Label Adherence

The cumulative incidence of stroke and systemic embolism, major bleeding, intracranial bleeding, gastrointestinal bleeding, acute myocardial infarction and all-cause death is shown in Figure 3. There was a significantly higher rate of stroke and systemic embolism, major bleeding, gastrointestinal bleeding, and all-cause death in patients with NOAC overdosing in comparison with labeled use or underdosing.

In reference with labeled use group, the adverse event in terms of stroke and systemic embolism were higher in overdosing group (5.76 versus 4.03 events/100 patient-years; hazard ratio [HR], 1.45; 95% CI, 1.01–1.34; adjusted HR [aHR], 1.16; 95% CI, 1.01–1.34) (Figure 4). Major bleeding was significantly higher in the overdosing group (4.77 versus 2.94 events/100 patient-years; HR, 1.63; 95% CI, 1.39–1.90; aHR, 1.18; 95% CI, 1.01–1.38). Mortality was also significantly higher in the overdosing group (5.43 versus 3.05 events/100 patient-years; HR, 1.81; 95% CI, 1.56–2.09; aHR, 1.19; 95% CI, 1.02–1.38). The incidence rates of intracranial bleeding, gastrointestinal bleeding, or acute myocardial infarction were comparable between overdosing and labeled use group (Figure 4). On the other hand, underdosing was not associated with worse clinical outcomes in comparison with labeled NOAC use (Figure 5).

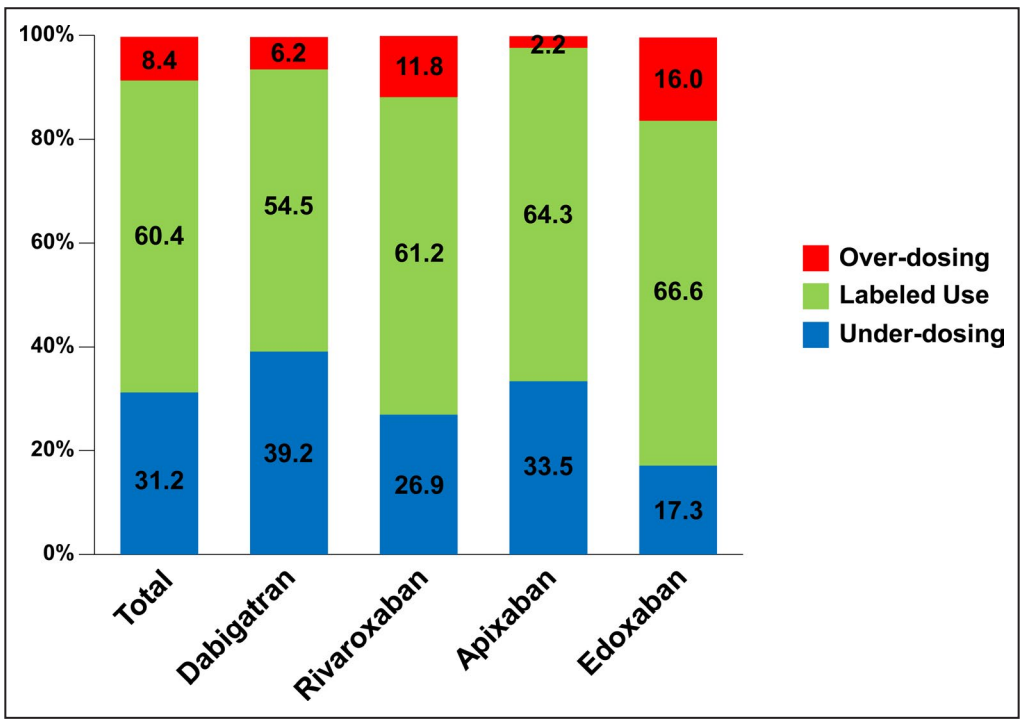

Figure 2. Label adherence of NOAC dosing.

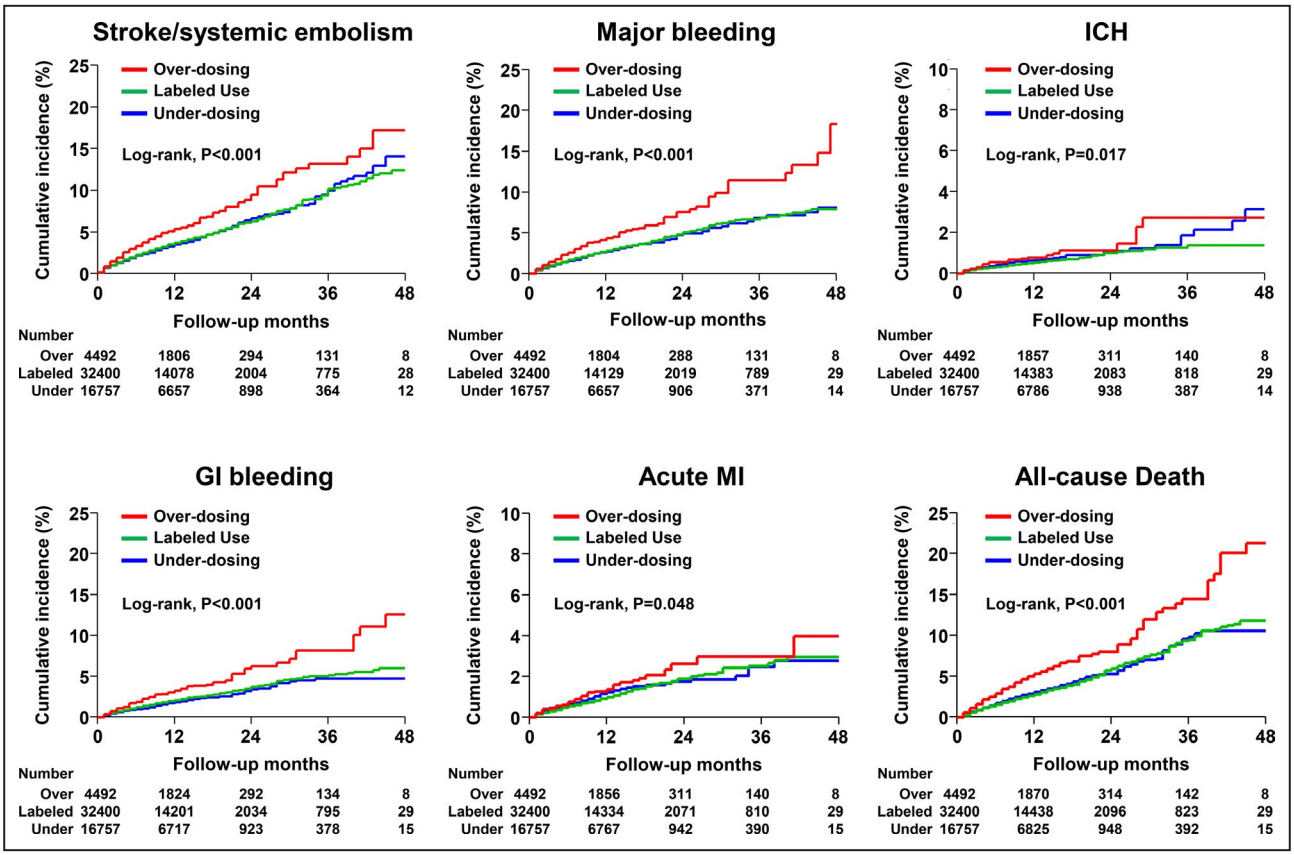

Figure 3. Cumulative incidence of clinical outcomes according to label adherence.
ICH indicates intracranial bleeding; and MI, myocardial infarction.

The effectiveness and safety outcomes of 4 individual NOACs in terms of over-/underdosing were also assessed (Figure S1). In reference with labeled use group, overdosing of dabigatran was associated with increasd risk of major bleeding (aHR, 1.39; 95% CI, 1.04–1.88) and gastrointestinal bleeding (aHR, 1.52; 95% CI, 1.10–2.11). Overdosing of apixaban was associated with increased risk of gastrointestinal bleeding (aHR, 1.83; 95% CI, 1.04–3.24) and all-cause death (aHR, 1.72; 95% CI, 1.10–1.88). In addition, underdosing of rivaroxaban was associated with increasd risk of all-cause death (aHR, 1.37; 95% CI, 1.16–1.63) compared with labeled use of rivaroxaban.

DISCUSSION

In the current study, we analyzed the label adherence of NOAC dosing across four NOACs and the associations between off-label NOAC dosing and clinical outcomes in patients with AF in routine clinical practice. We found that off-label NOAC dosing was not uncommon in the real-world practice: 31% NOAC-treated patients were underdosed, 8.4% were overdosed, and 60% were dosed appropriately according to drug labeling. Compared with patients with label adherence, those who were underdosed or overdosed were older, more likely female, and had a higher CHA_2DS_2-VASc scores. According to the current analysis, underdosing was not associated with worse clinical outcomes in comparison with labeled NOAC dosing, but there was no benefit in terms of safety either. However, NOAC overdosing was associated with increased risk for stroke or systemic embolism, major bleeding, and all-cause mortality compared with label-adherent dosing. These findings could give us meaningful messages of the real-world NOAC dosing patterns in patients with AF.

Label Adherence of NOAC Dosing in Real-World Practice

The appropriate dosing of NOACs for stroke prevention in AF has become an important issue. Currently, there are several data on the prescribed doses of NOACs in clinical practice of stroke prevention in AF. In a small Australian analysis, inappropriate NOAC dosing was identified in 34% and renal dysfunction was the primary driver of inappropriate dosing for those patients.[20] In larger analysis, in the ORBIT-AF II registry, 9.4% were underdosed, 3.4% were overdosed, and 87% were dosed according to US labeling.[10] Using a

	Event No.	IR, %/Year	HR (95% CI)	Adjusted HR (95% CI)	P-value*
S/SE					
Labeled use	1,196	4.03	Reference	Reference	
Over-dosing	235	5.76	1.45 (1.26-1.67)	1.16 (1.01-1.34)	0.042
Major bleeding					
Labeled use	884	2.94	Reference	Reference	
Over-dosing	194	4.77	1.63 (1.39-1.90)	1.18 (1.01-1.38)	0.042
ICH					
Labeled use	172	0.54	Reference	Reference	
Over-dosing	37	0.89	1.58 (1.11-2.25)	1.27 (0.88-1.82)	0.202
GI bleeding					
Labeled use	653	2.18	Reference	Reference	
Over-dosing	146	3.65	1.65 (1.38-1.98)	1.17 (0.97-1.40)	0.093
Acute MI					
Labeled use	327	1.09	Reference	Reference	
Over-dosing	61	1.55	1.37 (1.05-1.81)	1.01 (0.76-1.33)	0.950
All-cause death					
Labeled use	897	3.05	Reference	Reference	
Over-dosing	222	5.43	1.81 (1.56-2.09)	1.19 (1.02-1.38)	0.024

Figure 4. Incidence rates and hazard ratios of clinical outcomes in the overdosing group. Each HR was adjusted for age, sex, chronic kidney disease, dyslipidemia, and other risk factors included in CHA_2DS_2-VASc risk score factors (heart failure, hypertension, diabetes mellitus, stroke or transient ischemic attack, and vascular disease).
HR indicates hazard ratio; ICH, intracranial bleeding; IR, incidence rate; MI, myocardial infarction; and S/SE, stroke or systemic embolism. **P* value for adjusted HR.

large US claims database with 14 865 patients, Yao et al[11] reported that 43.0% were potentially overdosed among the patients with a renal indication for dose reduction, and 13.3% were potentially underdosed among the patients with no renal indication for dose reduction. The use of low-dose NOAC is known to be more frequent among Asian AF patients. In Taiwanese nationwide data, 87% and 90% of the total study subjects were shown to be taking low-dose rivaroxaban (10–15 mg once daily) and dabigatran (110 mg twice

	Event No.	IR, %/Year	HR (95% CI)	Adjusted HR (95% CI)	P-value*
S/SE					
Labeled use	1,196	4.03	Reference	Reference	
Under-dosing	584	4.00	0.98 (0.89-1.08)	1.00 (0.91-1.10)	0.996
Major bleeding					
Labeled use	884	2.94	Reference	Reference	
Under-dosing	442	2.97	1.00 (0.89-1.12)	0.99 (0.88-1.11)	0.819
ICH					
Labeled use	172	0.54	Reference	Reference	
Under-dosing	109	0.80	1.27 (0.99-1.61)	1.24 (0.97-1.59)	0.087
GI bleeding					
Labeled use	653	2.18	Reference	Reference	
Under-dosing	299	2.05	0.92 (0.80-1.05)	0.91 (0.79-1.04)	0.157
Acute MI					
Labeled use	327	1.09	Reference	Reference	
Under-dosing	186	1.26	1.14 (0.95-1.37)	1.09 (0.91-1.31)	0.334
All-cause death					
Labeled use	897	3.05	Reference	Reference	
Under-dosing	472	3.20	1.07 (0.95-1.19)	1.07 (0.96-1.20)	0.243

Figure 5. Incidence rates and hazard ratios of clinical outcomes in the underdosing group.
Each HR was adjusted for age, sex, chronic kidney disease, dyslipidemia, and other risk factors included in CHA_2DS_2-VASc risk score factors (heart failure, hypertension, diabetes mellitus, stroke or transient ischemic attack, and vascular disease). HR indicates hazard ratio; ICH, intracranial bleeding; IR, incidence rate; MI, myocardial infarction; and S/SE, stroke or systemic embolism. **P* value for adjusted HR.

daily), respectively.[21] In a recent Korean report using the Comparison Study of Drugs for Symptom Control and Complication Prevention of AF (CODE-AF) registry,[22] the label adherence of NOAC dosing was about 60%, and more than one third of patients with NOAC prescription received an off-label reduced dose. However, neither studies reported the clinical outcome according to inappropriate NOAC dosing. In the present study, we first reported the real-world label adherence of NOAC dosing across all 4 NOACs and their clinical effects in Asian AF patients.

Clinical Implication of Label Adherence of NOAC Dosing

There are several studies that have reported clinical outcomes according to label adherence of NOAC dosing. Previously we reported lower relative effectiveness for the prevention of thromboembolic events with low-dose edoxaban regimen (30 mg daily) compared with warfarin in patients with a creatinine clearance >95 mL/min in real-world setting.[12] In that study, a 30-mg dosage of edoxaban was used in 31% of patients with supranormal renal clearance and ≈40% of patients were using lower doses of edoxaban inappropriately when analyzed based on body weight and creatinine clearance criteria of label-recommended edoxaban dosing. In the ORBIT-AF II registry, NOAC over- and underdosing were associated with increased risk for adverse events such as stroke or systemic embolism, myocardial infarction, major bleeding, and all-cause mortality compared with the recommended dosing of NOACs.[10] Especially, inappropriate dose reduction of NOAC was associated with a reduced effectiveness for stroke prevention without any safety benefit.[11] Recently, a meta-analysis of pivotal randomized controlled trials showed that NOACs had an improved benefit-harm profile compared with warfarin when appropriately dose-adjusted.[23] Efficacy and safety of reduced-dose NOACs compared with warfarin in patients eligible for reduced-dose NOACs were consistent with those of full-dose NOACs relative to warfarin in those eligible for full-dose NOACs. In our current study, the adverse clinical consequence was higher in the overdosing group compared with the on-label dosing group, and there was no safety benefit of underdosing compared with the appropriate dosing of NOACs. Based on the results so far, label adherence of NOAC dosing is important to improve the clinical outcomes in AF patients, and further investigation is needed to assess the optimal dosing of NOACs in the Asian AF population.

Study Limitations

There are several limitations in the present study. First, we classified NOAC dosing groups based on patients' baseline clinical characteristics, there is the possibility that other confounding factors and changes in patient status during the follow-up period may have influenced the physician's prescription decisions. Especially changes in NOAC dosing during the follow-up period was not captured in the present analysis, which may in turn affect the findings of the study. Second, the poor clinical outcome of patients in overdosing group might be affected by their older age and higher prevalence of comorbidities, although the NOAC dosing label already reflects factors such as age, body weight, and kidney function. However, because we thought that differences in base characteristics and comorbidities such as patient age or renal function were important factors in determining appropriate NOAC dosing, we present the analysis without matching among groups to show the results as they are in the real world practice setting. Finally, the present nationwide study only enrolled the entire Korean population, whether the results can be extrapolated to other populations remains uncertain. Despite these limitations, our findings reflect the real-world practice pattern of NOAC dosing in Asian AF patients and the clinical consequences of label adherence of NOAC dosing.

CONCLUSIONS

In routine clinical practice, a significant proportion of AF patients received NOAC doses inconsistent with drug labeling. NOAC overdosing is associated with increased risk for stroke or systemic embolism, major bleeding, and all-cause mortality in Asian AF patients. NOAC underdosing was not significantly associated with increased risk of stroke, but there was no safety benefit in comparison with label-adhered NOAC dosing.

ARTICLE INFORMATION

Received January 7, 2020; accepted May 5, 2020.

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Acknowledgments

The National Health Information Database was provided by the NHIS of Korea (NHIS-2018-4-025). The authors thank the NHIS for its cooperation.

Sources of Funding

This study was supported by a research grant from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (NRF-2017R1A2B3003303, 2017R1C1B1008292) and grants from the Korean Healthcare Technology R&D project funded by the Ministry of Health & Welfare (HI16C0058, HI15C1200).

Disclosures

Dr Lip has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo and as a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim,

and Daiichi-Sankyo. No fees are directly received personally. Dr Joung has served as a speaker for Bayer, BMS/Pfizer, Medtronic, and Daiichi-Sankyo and has received research funds from Medtronic and Abbott. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S3
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Definitions and ICD-10 codes used for defining the comorbidities.

Comorbidities	Definitions	ICD-10 codes or conditions
Heart failure	Defined from diagnosis*	ICD10: I11.0, I50, I97.1
Diabetes mellitus	Defined from diagnosis* plus treatment	ICD10: E10, E11, E12, E13, E14 Treatment: all kinds of oral antidiabetics and insulin.
Ischemic stroke	Defined from diagnosis*	ICD10: I63, I64
Hemorrhagic stroke	Defined from diagnosis*	ICD10: I60, I61, I62
Myocardial infarction	Defined from diagnosis*	ICD10: I21, I22, I25.2
Peripheral arterial disease	Defined from diagnosis*	ICD10: I70.0, I70.1, I70.2, I70.8, I70.9
Chronic kidney disease	Defined from eGFR (if laboratory value was not available, diagnosis code was used)	eGFR <45 mL/min per 1.73 m^2 (ICD10: N18, N19)
Dyslipidemia	Defined from diagnosis*	E78

*To ensure accuracy, comorbidities were established based on one inpatient or two outpatient records of ICD-10 codes in the database.

ICD-10, International Classification of Diseases-10th Revision; eGFR, estimated glomerular filtration rate.

Table S2. The dose-adjustment criteria for the NOACs under the Korean labeling and the criteria used in the phase 3 RCT.

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Standard dose	150 mg twice daily	20 mg once daily	5 mg twice daily	60 mg once daily
Dose reduction criteria: Phase 3 RCT		15mg once daily if CrCl 30-49 mL/min	2.5 mg twice daily, if at least 2 of age ≥80 years, body weight ≤60kg or serum creatinine level ≥1.5 mg/dL	30 mg once daily, if any of the following: CrCl of 30-50mL/min, body weight ≤60 kg, concomitant use of verapamil or quinidine or dronedarone
Dose reduction criteria: Korean label	110 mg twice daily, if any of the following: CrCl 30-50 mL/min, age ≥75 years	15mg once daily if CrCl 15-49 mL/min	2.5 mg twice daily, if at least 2 of age ≥80 years, body weight ≤60 kg or serum creatinine level ≥1.5 mg/dL 2.5 mg twice daily, if CrCl 15-29 mL/min	30 mg once daily, if any of the following: CrCl of 15-50mL/min, body weight ≤60 kg, concomitant use of p-glycoprotein inhibitors

CrCl, creatinine clearance; RCT, randomized clinical trial

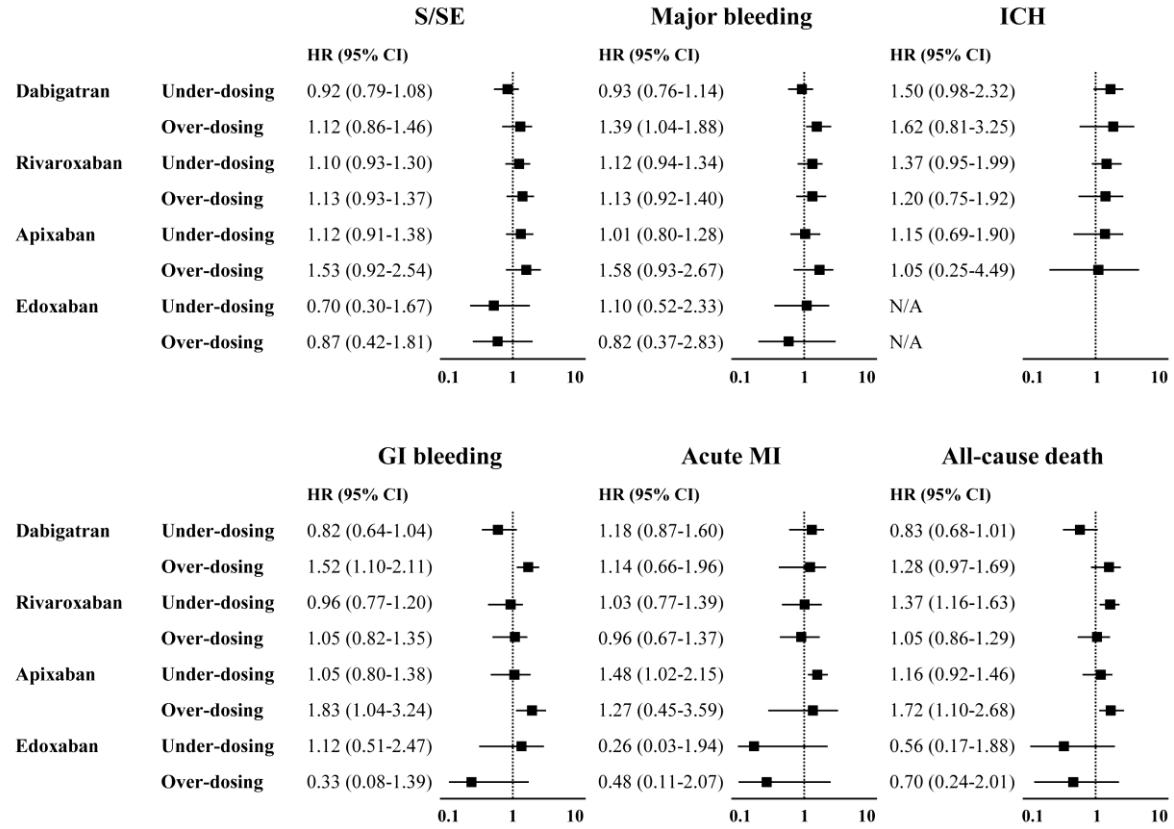
Table S3. Definitions and ICD-10 codes used for defining the outcomes.

Outcomes	Definitions	ICD-10 codes
Ischemic stroke	Defined from diagnosis of ischemic stroke with concomitant imaging studies of the brain or related death	I63, I64
Systemic embolism	Defined from admission diagnosis or related death	I74, N280 (including renal infarction)
Intracranial hemorrhage (ICH)	Defined from admission diagnosis of ICH with concomitant imaging studies of the brain or related death	I60-I62
Gastrointestinal bleeding	Defined from admission diagnosis or related death	K25-28 (subcodes 0-2 and 4-6 only), K92.0, K92.1, K92.2, K62.5, I85.0, I98.3
Major bleeding	ICH, gastrointestinal bleeding, or anemia caused by bleeding	I60-I62, K25-28 (subcodes 0-2 and 4-6 only), K92.0, K92.1, K92.2, K62.5, I85.0, I98.3, D62
Acute myocardial infarction	Defined from admission diagnosis of AMI with concomitant use of dual antiplatelet therapy or related death	I21, I22
Heart failure admission	Defined from admission diagnosis (including only main and first sub-diagnosis)	I11.0, I50, I97.1

*To ensure accuracy, comorbidities were established based on one inpatient or two outpatient records of ICD-10 codes in the database.

ICD-10, International Classification of Diseases-10th Revision.

Figure S1. The effectiveness and safety outcomes of 4 individual NOACs in terms of over-/under-dosing.



HR, hazard ratio; S/SE, stroke or systemic embolism; ICH, intracranial bleeding; GI, gastrointestinal; MI, myocardial infarction. Each hazard ratio was assessed in reference with labeled use of same NOAC.